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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/618,178	07/18/2000	Stephen E. Lincoln	13151-2	9015

23719 7590 02/05/2007

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
2 MONTHS	02/05/2007	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/618,178
Filing Date: July 18, 2000
Appellant(s): LINCOLN ET AL.

J. David Ellett, Jr.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 17, 2006 appealing from the Office action mailed October 12, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Kimpton et al., "Automated DNA profiling employing multiplex amplification of short tandem repeat loci" PCR Methods and Applications, vol 3 (1993) pp. 13-22

Ledwina et al. "Testing for Hardy-Weinberg Equilibrium", Biometrics, vol 36 (March 1980), pp. 161-165

Jeanpierre, M. "Hazard and probabilities of unknown genotypes" Ann. Human Genetics, vol 56 (1992) pp. 325-330

WO 92/15712 GOULET et al 09-1992

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 75-82, 85, 86, 91-93, 95, 96-98, 102, 106-109 and112-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22) in view of Ledwina et al (Biometrics (1980) 36:161-165) and further as motivated in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330).

Kimpton teaches a method of claims 75 and 96 of determining the genotype at a locus within genetic material obtained by PCR amplification from a subject (page 14) comprising:

a) Reacting the material at the locus to produce a first reaction value (see page 14, columns 1-3, subheading "Locus specific amplification conditions"),

b) forming a data set including the first reaction value by assembling reaction value data points for the samples, each reaction-value data point corresponding to a respective one of the samples and including at least one reaction value (here the data points represented by each of the separate peaks in figure 1 represents a different sample and are assembled in figure 2) (see pages 14-16),

e) determining the genotype and confidence score for each reaction value data point, thus determining the genotype and confidence score at the genetic locus for each sample (here, table 2 on page 17 provides for each reaction point the genotype and a standard deviation based on the data obtained from step d) (page 16 and page 17).

With regard to claim 77 and 78, Kimpton expressly teaches reacting the material at multiple loci (page 14, table 1).

With regard to claims 80-82, 114, 115, on page 17, Kimpton expressly considers multiple alleles in the probability distributions, particularly in table 2 which expressly notes that the method is applicable to any number of alleles.

With regard to claim 85, 97, 98, 108, 109, Kimpton teaches confidence score determination (see pages 16 and 17).

With regard to claim 86, 102, 107, Kimpton expressly selected the loci for their discrimination ability and teaches that several different loci may be analyzed (page 16, column 1).

With regard to claims 91-93, Kimpton expressly teaches the use of multiple data points derived from multiple runs of the automated apparatus including multiple data sets in the exemplified method and apparatus (page 16, especially figure 2).

With regard to claim 95, Kimpton expressly teaches that the locus may be dinucleotide or tetranucleotide repeats (page 13).

With regard to claim 112, Kimpton teaches obtaining data that correlates the reaction value to the genotype (see pages 16 and 17).

With regard to claim 113, Kimpton demonstrates optical signals (see figure 1, where dye labeled DNA products are detected).

While Kimpton uses the Hardy-Weinberg test, Kimpton does not establish a distribution set of probability distributions and Kimpton does not then apply the reaction value of the distributions to detemine a measure of a conditional probability of each genotype of interest at the locus.

Ledwina teaches a method in which genotypes can be determined in which the Hardy Weinberg test is modified such that the steps of:

c) establishing a distribution set of probability distributions and associating hypothetical values with corresponding probabilities for each genotype of interest (see page 162 and page 163),

d) applying the first value to each pertinent probability distribution to determine a measure of conditional probability of each genotype of interest (see page 162 and page 163, especially "conditional distribution of T given Z=z" equation on page 163).

With regard to claim 76 and 79, Ledwina teaches a plurality of distributions which are hypothetical (see page 162, "common probability distribution of (T,Z) is multinomial with 1/2m(m+1) cells and with the vector of cell probabilities g=(g...).".

Further, JeanPierre motivates the use of computation of unknown genotypes to analyze the conditional probabilities relative to a distribution of hypothetical reaction values (see page 330).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Kimpton to use the conditional probability distribution method of Ledwina since Kimpton notes that the anlaysis uses the Hardy-Weinberg equilibria (see abstract) and since Ledwina states "The class of admissible tests for Hardy-Weinberg equilibrium in a multi allelic system is characterized. The standard goodness of fit chi square test is shown to be admissible for systems of two or more alleles. The conditional probability distribution required to determine the exact significance level of this test is presented (see abstract)". An

ordinary practitioner would have been motivated to apply this hypothetical distribution analysis to genotyping since Jeanpierre notes the gains from creating such a distribution include avoiding hazards such as incorrectly using the simple average of the conditional probabilities instead of the harmonic mean, to more accurately determine the genotype (see page 330).

Claims 75-82, 85-87, 91-98, 100, 102, 106-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22) in view of Ledwina et al (Biometrics (1980) 36:161-165) and further as motivated in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330) and further in view of Goulet et al.

Kimpton in view of Ledwina as motivated by JeanPierre teach the limitations of claims 75-82, 85, 86, 91-93, 95, 96-98, 102, 106-109 and 112-115 as discussed above. Kimpton in view of Ledwina as motivated by JeanPierre does not teach genetic bit analysis, which includes allele specific amplification, nor the particular alleles listed.

Goelet teaches genetic bit analysis methods, including allele specific amplification methods (see entire document, expecially pages 10-13). Goulet teaches single specific nucleotide alleles (see page 40, example 3). Goulet also shows a mutation which is associated, at least indirectly, with a restriction site (see figure 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Kimpton in view of Clark with the use of genetic bit analysis or allele specific amplification to develop the data since Goelet states "The current invention provides a method that can be used to diagnose or characterize nucleic acids in biological samples without recourse to gel electrophoretic

size separation of the nucleic acid species. This feature renders this process easily adaptable to automation and thus will permit the analysis of large numbers of samples at relatively low cost (page 8, lines 27-33)". An ordinary practitioner would have been motivated to substitute the equivalent genetic bit analysis method for PCR in order to minimize the need for gel electrophoresis and enhance the automatability of the process as expressly motivated by Goulet in order to speed analysis and minimize costs.

Claim Rejections - 35 USC § 112 – second paragraph

Claim 94 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The new amendment, which results in claim 94 stating "wherein step (A) includes the step of assaying for the given allele using genetic bit analysis, allele specific hybridization, or allele specific amplification, including such amplification by a polymerase chain reaction or a ligase chain reaction" is vague and indefinite. The claim is indefinite because it is unclear to what "such amplification" is referring, since both genetic bit analysis and allele specific amplification require extension by a polymerase. Essentially, it is unclear what is added by the final phrase "such amplification" since the phrase lacks clear antecedent basis. Correction is required.

(10) Response to Argument

Introduction

This application is drawn to performing an ordinary assay and applying standard and well known statistical techniques to that assay. The prior art is replete with references teaching methods of genotyping by analyzing nucleic acid variations. The cited reference, Kimpton, is one among thousands who determine genotypic information and then perform statistical analyses. It is also standard operating procedure to analyze biological data using known statistical techniques.

Issue 1 - Do the teachings of Kimpton in view of Ledwina and Jeanpierre render the claims prima facie obvious?

Legal Standard

The legal standard for obviousness is based upon the factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Prima Facie Case

Kimpton teaches each limitation of the claims except probability distributions with conditional probabilities

As the following analysis (and that shown in the rejection) demonstrate, Kimpton teaches each and every limitation of the claims rejected under 35 U.S.C. 103 except for the conditional probability analysis.

Claim 75	Kimpton
A method of determining the genotype of a subject at a locus within genetic material obtained from a biological sample from the subject, the method comprising:	"In addition to their suitability for mapping and linkage analysis, STRs provide a source of highly informative loci for use in the identification of individuals. DNA profiling based on PCR amplification of STRs has the advantage of being more sensitive than conventional techniques." (see page 13, column 3, for example)
A. reacting the material at the locus to produce a first reaction value indicative of the presence of a given allele at the locus;	See page 14 for reaction conditions and see page 16, column 1, "Fourteen 3- to 5-bp STR loci were selected for evaluation based on their predicted discrimination power, as indicated by data published previously (for references, see Table 1). STR amplification products were tagged

	by the attachment of a fluorescent dye molecule to one of each pair of locus-specific primers. Amplified products were then detected by laser scanning during electrophoresis on denaturing polyacrylamide gels. Band sizes were generated automatically by comparison with a standard sizing ladder included in every sample prior to electrophoresis."
B. forming a data set including the first reaction value;	"Allele frequencies for each STR locus under investigation were determined from a minimum of 50 random individuals for each of three different populations: Caucasians, Afro-Caribbeans, and Asians. Allele frequency histograms for all 14 loci are shown in Figure 3. Symmetrical and skew unimodal, bimodal and more complex distributions, were observed among the 14 loci. Differences in allele frequencies among population groups were also seen." (see page 17, column 1).

C. establishing a distribution set of probability distributions, including at least one distribution, associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus;	"The data sets were tested for Hardy-Weinberg equilibria using a log likelihood-G test. In total, 42 locus population comparisons were carried out. Deviation from Hardy-Weinberg equilibria was only detected for the HUMC- YARO3 Caucasian data ($P < 0.05$)." (see page 17, column 2).
D. applying the first reaction value to each pertinent probability distribution to determine a measure of a conditional probability of each genotype of interest at the locus; and	Taught by Ledwina as discussed below.
E. determining the genotype based on the data obtained from step (D).	"In conclusion, tri-, tetra-, and penta-nucleotide STR loci appear to be well suited for routine identification of individuals. (see page 21, column 1)."

As discussed in the rejection, while Kimpton applies the Hardy-Weinberg test to analyze the genotypic data, Kimpton does not teach the use of conditional probabilities required by step D. Ledwina teaches a method in which genotypes can be determined in which the Hardy Weinberg test is modified such that the steps of:

c) establishing a distribution set of probability distributions and associating hypothetical values with corresponding probabilities for each genotype of interest (see page 162 and page 163),

d) applying the first value to each pertinent probability distribution to determine a measure of conditional probability of each genotype of interest (see page 162 and page 163, especially "conditional distribution of T given Z=z" equation on page 163).

Jean-Pierre motivates the use of such conditional probability analysis in direct genotypic analysis and bridges the gap of population genetics and individual analysis using conditional probability and the Hardy-Weinberg equalibrium as discussed in the rejection.

Population versus Individual

Appellant's first series of arguments revolve around a perceived difference between the analysis of populations and individuals. Appellant argues at pages 15-17 of the brief that the Hardy-Weinberg analysis is drawn to populations and not to individual genotypes. However, the use by Kimpton of the Hardy-Weinberg equilibrium analysis is precisely the analysis necessary for the claims and necessary to determine the allelic information of a particular individual. That is, Kimpton determines the distribution of the alleles throughout a population. While Kimpton does not project "conditional probabilities" for possible genotypes, prior to determination of alleles in individuals, the presence of the alleles in the population must be determined or there will be no basis to differentiate individuals from one another. Kimpton performs this

primary step of creating the population data. Kimpton then directly suggests and teaches that this population data may be used to provide individual genotypic information (e.g. "In conclusion, tri-, tetra-, and penta- nucleotide STR loci appear to be well suited for routine identification of individuals (page 21 of Kimpton)").

Consequently, when Appellant argues that the Hardy-Weinberg data is not used for analysis of individual genotypes, this is directly contradicted by Kimpton who requires a discriminatory database created with the Hardy-Weinberg test before individual identification can be performed (see page 20, column 3, paragraph 3, for clear example).

Further, when Appellant argues at page 18 that Kimpton does not analyze multiple alleles, it is unclear what Appellant is reviewing. Tables 3 and 4 of Kimpton expressly disclose analysis of multiple alleles. Table 4, in particular, is drawn to pM (or matching probability) analysis, regarding which Kimpton notes "Discriminating power and matching probabilities (pM) were calculated by the method of Jones (see page 15, column 1)." Table 4 expressly multiplexes 4 to 7 different alleles and calculates a combined pM value for each multiplex analysis.

Hypothetical reaction values

Appellant then argues, at pages 20-40, that because Kimpton's method accurately measured allele values, there would have been no motivation to perform the conditional probability analysis with the method of Kimpton. This argument is not found persuasive for several reasons. First, Kimpton expressly teaches that some alleles are

not as easily analyzed and require analysis of the distributions (see page 20, column 2), which is a direct suggestion to perform an analysis that will permit distribution analysis, such as the conditional probability analysis of Ledwina. Second, when Kimpton analyzes individual genotypes, Kimpton notes at page 20, column 3, that

> "The overall pM of the three multiplex systems developed was <1 x 10-14, thus highlighting the power of these systems for individual identification. However, before a discriminatory system is accepted for routine forensic use, it must be proved to be both robust and reliable. The high incidence of artifactual stutter bands observed with dinucleotide STR loci make them unsuitable for forensic applications."

This statement expressly teaches that in forensic applications, additional statistical analysis is necessary to distinguish artifactual stutter bands.

Jeanpierre recognizes that the conditional probability analysis can resolve the problem of inaccurate data, noting,

> "This paper presents a procedure for deriving the probability of a genotype from the probabilities conditional on the genotype that can be obtained from any risk calculation program. The expression of the risk as a function of the possible genotypes exposes a hazard of misinterpretation (see page 325)."

Consequently, the ordinary practitioner interested in improving the quality of the multiplex analysis, which Ledwina teaches requires conditional probability analysis, would have been motivated to use such a conditional probability analysis in the method of Kimpton, since Jeanpierre teaches that this analysis will improve the interpretation and accuracy of the analysis (also see page 329 and 330 of Jeanpierre).

Appellants fundamental disagreement is over this issue. The central argument is whether an ordinary practioner would have been motivated to apply the known

statistical methods, known by Jeanpierre to be applicable to analysis of individual genotypes, to the genotypic analysis method of Kimpton

This motivation is consistent with the requirements enunciated by the Federal Circuit in Dystar v. Patrick Co., 80 USPQ 2d 1641, 1651(Fed. Cir. 2006) noting,

> "Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references."

The Dystar court clarifies that motivation exists when the improvement results in a more desirable process and the issue then devolves to whether the ordinary artisan possesses the knowledge capable of combining the references. Here, where the ordinary practitioner is a Ph.D. with many years experience and where the improvement is the application of known statistical techniques to known mehtods, there is no doubt that the ordinary artisan possesses the knowledge and motivation sufficient to apply statistical techniques to biological data.

Appellant's attack on the Ledwina publications specific statistical techniques is again pointed towards the distinction between populations and individuals. The ordinary practitioner would recognize that the method is broadly applicable to either, since the

sole issue is the probability distribution of "random vector X", which could be either the population of individuals or the population of measured alleles in an experimental situation. If the latter population is analyzed, it will result in the conditional probability analysis of the particular genotype of an individual.

Claim 96 and 106

Appellants then argue that claims 96 and 106 differ from the combination of Kimpton, Ledwina and Jeanpierre because of the use of the phrase "genotypic classes". Since each allele may be deemed a "genotypic class" (the term is not defined by the specification), the allelic analysis of Kimpton is a "genotypic class" analysis. With regard to the conditional probability analysis of these "genotypic classes", the combination teaches such conditional probability analysis as already discussed.

Appellant also reiterates the reaction value argument which was addressed above.

Goelet rejections

Apellent separately argue Goelet based upon the arguments already made against Kimpton, Ledwina and Jeanpierre. Goelet is used solely to teach a particular known prior art method, and Appellant relies upon overcoming the primary rejection to overcome the further rejection involving Goelet.

Issue 2 - Is the term "such amplification" indefinite?

Legal Standard

In In re Corkill, 226 USPQ 1005 (Fed. Cir. 1985), the Federal Circuit confronted an issue similar to the current fact pattern. The Court notes "The Board agreed with the examiner's position that it was not clear whether the particle sizes in the '615 claims referred to single zeolite crystals or to agglomerates comprised of smaller crystals." Id. at 1009. The court sustained the rejection since the claim was indefinite as to the composition. As MPEP 2173.02 notes "Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite."

The phrase "such amplification" is insolubly ambiguous

In the context of claim 94, the phrase "such amplification" falls into that category of "insolubly ambiguous". The term lacks antecedent basis in claim 94 itself or in claim 75 from which claim 94 depends. This renders the claim insolubly ambiguous because the ordinary practitioner is entirely unable to determine what amplification is meant by "such amplification". As MPEP 2173.05(e) notes "Similarly, if two different levers are recited earlier in the claim, the recitation of "said lever" in the same or subsequent claim would be unclear where it is uncertain which of the two levers was intended." This is precisely identical to the current fact pattern, where the phrase "such amplification" is used, but the claim and the parent claim 75 contain multiple prior references to amplification. That is, while Appellant correctly notes that the term "allele specific amplification" occurs immediately preceding the phrase "such amplification", claim 94

also expressly discusses genetic bit analysis, which is a method that can use the polymerase chain reaction as shown by example 3 on page 40 of the Goulet reference. Consequently, the claim is indefinite because it is unclear to which prior method the phrase "such amplification" is referring, GBA or allele specific amplification. For this reason, the indefiniteness rejection is maintained.

Issue 3 - Priority Issue

The priority issue is not addressed here since the prior art cited is entirely before the earliest priority date and therefore is applicable irrespective of the priority date granted.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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PRIMARY EXAMINER
11/30/07

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